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Back

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3D model of Human Blood-Brain Barrier Microvascular Network including iPS-derived Endothelial Cells, brain Pericytes and Astrocytes

Marco Campisi[1], Yoojin Shin[2], Tatsuya Osaki[2], Valeria Chiono[3], Roger Kamm[2,4]
[1]Department of Mechanical and Aerospace Engineering, politecnico di Torino, Turin, Italy. [2]Department of Mechanical engineering, Massachusetts Institute of Technology, Cambridge, USA. [3]Department of Mechanical and Aerospace Engineering,politecnico di Torino, Turin, Italy. [4]Department of Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, USA

Abstract

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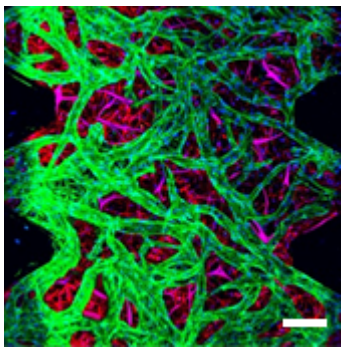
Introduction
The **blood-brain barrier (BBB)** is a complex structure necessary for separating the brain from systemic blood circulation maintaining neural homeostasis and protecting from harmful compounds. However, this selective barrier also prevents efficient drug delivery to specific brain areas, preventing treatments of neurodegenerative diseases and cancers[1]. Furthermore, traditional and animal models failed to reproduce the complexity of brain barriers, conducting to misleading results in clinical trials. To overcome those limitations, we developed an innovative **3-dimensional BBB self-organized microvascular network model** via vasculogenesis that accurately replicates the anatomical neurovascular organization observed *in vivo*.

Methods
A PDMS microfluidic model including human induced pluripotent stem cells (iPS)-derived endothelial cells, primarybrain pericytes, and astrocytes as self-assembled vascular networks. RT-PCR, vascular permeability and immunocytochemistry assays were performed.

Results
Gene expression of tight junctions (ZO-1, occludin, and claudin-5), extra-cellular matrix proteins (Laminin and Collagen IV), and membrane transporters (PG-P, LAT1, LRP1) was higher in tri-culture condition consistently with quantitative immunocytochemistry analysis indicating BBB-like maturation. Laser confocal microscopy validated microvessel-pericytes/astrocytes contact-interactions. Characterization of microvascular network parameters, as vascular diameter, branches length and vascular network area coverage were lower when including pericytes and astrocytes. This revealed that morphological changes were induced by not only the secretion of pro-angiogenic and vasculogenic growth factors but also contact signaling between cells.
The BBB model exhibited perfusable and selective microvasculature, showing permeability coefficient comparable to previous models, (10 kDa FITC-Dextran: $2.2\times10^{-}$

^{7} cm/s; 40 kDa FITC-Dextran: 8.9×10^{-8} cm/s).



Discussions
Our BBB microfluidic model has the advantages that all three cell types are seeded simultaneously into a single gel region, producing a perfusable vascular network with permeabilities lower than those of other published models[2]. The contribution of co-culture with pericytes and astrocytes also improved BBB formation and integrity and upregulation of tight junction proteins and membrane transporters by the iPS endothelial cells, highlighted as potential targets to enhance the penetration of drugs into the brain.

Conclusions
This robust 3D BBB microvascular network model could be potentially applied to patient-specific and neurodegenerative diseases modelling, offering a novel platform to study both drug transport for preclinical screening as well as neurovascular functions within a physiologically-relevant BBB microvasculature.

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References
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